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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,468	10/12/2001	Jorge DiMartino	12636-219	9964

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,468	DIMARTINO ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005 and 28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-54 and 56-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-54 and 56-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *03052005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II in the reply filed on March 14, 2003 is acknowledged.

Applicant's Supplemental Response Dated February 28, 2005

2. In the Response filed February 28, 2005, claims 59 and 70 were amended; and claims 71-86 were added. Claims 45-54 and 56-86 are pending. An action on the merits of claims 45-54 and 56-86 is contained herein below.

3. The rejection of claims 45-54 and 56 under 35 U.S.C. 103(a) as being unpatentable over Waller US 5,800,539 (Waller) in combination with Trotta et al. *Cancer Research*, **1981**, Vol. 41, pages 2189-2196 (Trotta); and Spaner US 6,258,357 (Spaner) is maintained for the reasons of record set forth in the Office Action dated September 22, 2004.

Rejections of Record Set Forth in the Office Action Dated September 22, 2004

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 45-54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waller US 5,800,539 (Waller) in combination with Trotta et al. *Cancer Research*, **1981**, Vol. 41, pages 2189-2196 (Trotta); and Spaner US 6,258,357 (Spaner).

6. Applicant's arguments filed January 28, 2005 have been fully considered but they are not persuasive. Applicant argues that Waller does not teach or suggest administering pentostatin to a transplant recipient before the transplantation and Trotta does not teach or suggest a method preventing GVHD in human patient by administering pentostatin within a predetermined time window before transplantation, but also fails to teach or suggest administering pentostatin at the specified dose.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 58-69 and 71-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification invites the skilled artisan to unduly experiment. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Breath of Claims

Claims 58-69 and 71-86 are drawn to a method for preventing or reducing the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant, comprising administering to the transplant recipient pentostatin in a pharmaceutically effective amount within a predetermined tine window after the transplantation.

Nature of Invention

The invention relates to methods for the prevention of graft-versus-host disease employing pentostatin.

State of the Prior Art

The examiner directs applicant to Waller U.S. Patent 5,800,539 (Waller); Trotta et al. *Cancer Research*, **1981**, Vol. 41, pages 2189-2196; and Spaner U.S. Patent 6,258,357 (Spaner) cited in the 103 rejection in the Office Action dated June 3, 2003 regarding the state of the art in GVHD treatment and prevention.

Level of Ordinary Skill in the Art

The level of ordinary skill in the ad is seen to be a M.D. experienced transplant surgery or a PhD in the field of biomedical research.

Level of Predictability in the Art /Amount of Direction Provided by the Inventor

Please note that a single embodiment may provide broad enablement in cases involving predictable factors, but more is required in cases involving unpredictable factors, such as chemical or physiological activity, see *Ex. parte Hitzeman*, 9 USPQ2d 1821. In the instant case, no experimental data or citations of relevant prior art are presented in support of applicant's assertion that GVHD is prevented by the administration of pentostatin after transplantation. There has not been advanced an adequate written description which embraces or correlates an art-recognized mode for preventing or reducing the incidence of HVGD. There are no examples in the prior ad wherein HVGD is prevented by the administration of pentostatin or any other therapeutically active agent following transplantation. Additionally, the instant

specification provides no guidance as to how the skilled artisan would address various factors of concurrent co-administration of an immunosuppressive agent and pentostatin. Such factors include but are not limited to:

1. determination of the effects of the combination of drugs as they relate to their collective primary action chemically,

2. determination of the chemical properties of the combination of drugs (e.g., regarding collective interaction with cell receptors, toxicity, absorption), and

3. determination of the physical or structure-activity relationship between the combination of the active ingredients including cellular sites of drug action and modification of the active ingredients.

Working Examples

There are no working examples demonstrating the prevention of HVGD by administering pentostatin after transplantation.

Quantity of Experimentation Needed to make and/or use the Invention Based on the Content of the Disclosure

There are no teachings in the prior art suggesting that pentostatin is able to prevent or reduce the risk of developing HVGD wherein pentostatin is administered to the patient after transplantation. To provide adequate support for the breadth of the claims, applicant would have to provide sufficient evidence that a population of individuals was treated with pentostatin after transplantation and that population did not develop or had a reduced occurrence of HVGD. Applicant has failed to correlate via art-recognized evidence or adequate support in the instant disclosure that HVGD is

prevented regardless of whether pentostatin is administered before or after surgery. As such, a skilled artisan would not recognize that pentostatin is capable of preventing HVGD by administering pentostatin after surgery.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 57 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waller US 5,800,539 (Waller) in combination with Trotta et al. *Cancer Research*, **1981**, Vol. 41, pages 2189-2196 (Trotta).

Claim 45 is drawn to a method for preventing or reducing the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant, comprising administering to the transplant recipient pentostatin in a pharmaceutically effective amount within a predetermined time window before the transplantation. Claims 57 and 70 depend from claim 45. Claims 57 and 70 further limit the time window before transplantation to 2 or 3 days.

Waller teaches a method of transplanting hematopoietic system reconstituting cells from a donor source into an allogeneic recipient comprising administering to the recipient, prior to the administration of the hematopoietic system reconstituting cells, an amount of mononuclear cells which are treat so as to render them incapable of proliferating and causing a lethal GVHD effect, but which are effective in enhancing subsequent engraftment of the hematopoietic system reconstituting cells in the recipient; and administering to the recipient an effective amount of hematoietic system reconstituting cells (column 3, lines 32-43). The mononuclear cells are treated with cytotoxic chemotherapeutic drugs to render the cells incapable of proliferating and causing GVHD (column 4, lines 66-67; column 5, line 1). Examples of cytotoxic chemotherapeutic drugs to be employed include but are not limited to mitomycin C, bleomycin, fludarabine, and doxirubicin (column 5, lines 1-15). The treated

mononuclear cells are administered to the recipient at any time prior to the administration of the hematopoietic system reconstituting cells. Any range of treatment, e.g., one to nine, two to eight, three to seven, one to two, one to three, zero to one, zero to two days, etc. are also provided (column 5, lines 38-48). The amount of treated mononuclear cells administered to the recipient range between 0.05×10^6 and 30×10^6 mononuclear cells/kg of recipient's body weight (column 5, lines 57-61). The treated mononuclear cells and hematopoietic system reconstituting cells are typically administered to the recipient in a pharmaceutically acceptable carrier by intravenous infusion (column 7, lines 1-6).

Waller differs from the instantly claimed invention in that Waller does not explicitly teach the administration of pentostatin; however, the deficiency would have been obvious to one of ordinary skill in the art at the time of the invention in view of Trotta.

Trotta teaches the use of adenosine deaminase inhibitors in the prevention of graft-versus-host disease in hematopoietic transplantation (page 2189, ABSTRACT; page 2194, column 2, paragraphs 2-3). Trotta teaches that DCF (pentostatin) is infused continuously at a concentration of 0.8 mg/ml for a 20-g mouse (page 2190, column 1, paragraph 3). The effects of DCF administration also provide a theoretical basis for a new approach to the treatment of diseases of the lymphoreticular system by bone marrow transplantation. The usefulness of such transplantation has been limited by severe GVHD, which is invariably fatal unless donor and recipient are perfectly matched at the major histocompatibility locus. Treatment of lethally irradiated mice with fetal liver

or newborn spleen cells supports the concept that graft-versus-host reactions might not ensue if postthymic T-cells were absent from the reconstituting tissue. The results imply that elimination of differentiated lymphoid cells from the engrafting stem cell population would allow bone marrow transplantation using cells from unrelated individuals. In addition to the treatment of diseases of hematopoietic and immunological function, such an approach might have additional application in the achievement of organ transplantation without immunological rejection. In light of the specific lymphocytotoxicity of DCF in vivo, either in vivo pretreatment of the donor or in vitro treatment of the graft with an Adase inhibitor might be selective in destroying postthymic T-cells. This result contrasts with the toxicity of current immunosuppressives to tissues outside of the lymphoid system, including bone marrow. The use of DCF to promote transplantation across major histocompatibility barriers is thus a reasonable hypothesis based on these data.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prevent or reduce the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant, comprising administering to the transplant recipient an adenosine deaminase inhibitor in a pharmaceutically effective amount within a predetermined time window before the transplantation as both Waller and Trotta teaches prevention of GVHD comprising administering an adenosine deaminase inhibitor (fludarabine and pentostatin, respectively). Motivation for the use of pentostatin for preventing GVHD in a patient who is a recipient of an organ or tissue transplant is provided by Trotta which teaches that infusion of a low concentration of

DCF is specifically toxic to both B- and T-lymphocytes but does not impair the capacity of bone marrow stem cells to repopulate the hematopoietic system of lethally irradiated mice; these results may be directly applicable to the elimination of graft-versus-host reaction in humans as well as to the achievement of immunosuppression without toxicity to bone marrow and other proliferating cells (page 2189, column 2, last paragraph).

Conclusion

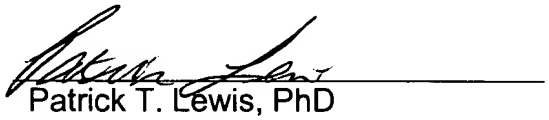
13. Claims 45-54 and 56-86 are pending. Claims 45-54 and 56-86 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patrick T. Lewis, PhD
Examiner
Art Unit 1623

ptl